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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/155,708	04/05/99	FARRAR G	MUR-7520

HM22/0213

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EXAMINER	
EPPS, J	
ART UNIT	**PAPER NUMBER**
1635	12

DATE MAILED: 02/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/155,708	Applicant(s) FARRAR ET AL.	
	Examiner Janet L Epps	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 1999* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Drawings

1. The drawings filed 4-05-1999 are objected to by the Draftsperson under 37 CFR 1.84 or 1.152 for the reasons cited on the attached PTO-948.

Sequence Information

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

3. A complete response to this Office Action requires that Applicants comply with the sequence rules, and that pending rejections be addressed. Any response that does not address all of these issues will be held as non-responsive. Direct the reply to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the reply.

Claim Objections

4. Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 8 recites "wherein suppressor(s) or replacement gene(s) are administered alone or in vector(s)", this limitation does not further limit claim 6 since according to claim 6 the suppression effector as well as the replacement nucleic acids are administered in vectors.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1, 5-9 and 11 provide for a strategy for suppressing or partially suppressing an endogenous gene and replacing the suppressed gene sequence with a nucleic acid sequence that differs from the endogenous gene; and for the use of a strategy in the preparation of a medicament, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 1, 5-9 and 11 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

7. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are the steps required for suppressing or partially suppressing an endogenous gene.

8. Claims 1 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "wherein the suppressing agent(s) comprises at least one suppressor from the group comprising antisense nucleic acid, peptide nucleic acids, DNA capable of forming triple helix or ribozymes targeted to the endogenous gene or gene transcripts." This statement is vague and indefinite since it appears to claim a Markush group without the proper use of the Markush format. Alternative expressions are permitted if they present no uncertainty or ambiguity with respect to the question of scope or clarity of the claims. One acceptable form of alternative expression, which is commonly referred to as a Markush group, recites members as being "selected from the group consisting of A, B and C." See Ex parte Markush, 1925 C.D. 126 (Comm'r Pat. 1925). Additionally, this phrase renders the scope of this claim vague and indefinite since it is unclear what other suppressors are included in this group.

Claim 11 recites the limitation "[a] use" in claim 1. There is insufficient antecedent basis for this limitation in the claim. Additionally, claim 11 reads on a method wherein "the replacement gene is altered from the wild type gene", the use of the term "altered" in this context is vague and indefinite since claim 1 clearly states that the

replacement gene is only modified at third base wobble positions so that it still encodes the wild type protein.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3 and 11 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims read on a method or strategy for suppressing or partially suppressing an endogenous gene and replacing the suppressed gene sequence with a nucleic acid sequence that differs from the endogenous gene, and further wherein the replacement gene is altered from the wild type gene and provides a beneficial effect when compared to the wild-type gene.

The medicaments and methods of use of the instant invention imply *in vivo* applicability for enablement purposes. However, the specification as filed does not provide sufficient guidance and/or instruction that would allow one of skill in the art to use the claimed invention throughout the full scope of the claims.

The instead method or strategy encompasses the *in vivo* nucleic acid in the treatment of a patient. However, It is well established in the art that there is a significant level of unpredictability regarding the behavior of nucleic acid base therapeutics.

According to Crooke (1998), states that "extrapolations from in vitro uptake studies to predictions about *in vivo* pharmacokinetic behavior are entirely inappropriate". Furthermore, Crooke teaches that variations in cellular uptake and distribution of oligonucleotide based therapeutics are influenced by a variety of factors: length of oligonucleotide, modifications, sequence of oligonucleotide and cell type. Crooke also describes several "non-antisense effects", for example some oligonucleotides tend to bind to many proteins protein binding in general by oligonucleotides may influence cell uptake, distribution, metabolism and excretion. Such protein binding may produce effects that can be mistakenly interpreted as antisense activity, and such binding may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, will be influenced by the chemical class of oligonucleotide studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of nucleic acid based compounds thereby rendering the activity of antisense or ribozyme based compounds unpredictable, and thus much experimentation is required to screen multiple antisense compounds to determine not only their efficacy *in vitro* but also *in vivo.*

Branch (1998) also teach that "the antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target-often through an entirely unexpected mechanism." In addition, Branch teaches that the successful delivery of nucleic acid therapeutics to their specified target *in vivo* is unpredictable, the internal structures of

the targeted RNAs and their association with cellular proteins can render target sites totally unaccessible *in vivo*. Nucleic acid based therapy is a highly unpredictable and field and the skill in the art is high.

Both Branch and Crooke teach that the behavior of nucleic acid based pharmaceuticals are unpredictable, therefore claims to nucleic acid based pharmaceuticals and methods of treating diseases by the administration of said pharmaceuticals are subject to the question of enablement due to the high level of unpredictability in the nucleic acid based therapy art.

The instant methods also read on a method of gene therapy. In regards to the level of unpredictability in the gene therapy art, multiple reviews indicate that efficient delivery and expression of foreign DNA has not yet been achieved by any method. Marshall (*Science*, 269:1050-1055, August, 1995) states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, column 1) and that "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field" (page 1054, column 3). Additionally, 5 years later scientists in the gene therapy field still conclude, "major problems remain to be solved before these approaches (referring to gene therapy techniques) can become effective and common place strategies for cancer. Principle among these (problems) is the basic ability to deliver therapeutic genes quantitatively, and specifically, not only into tumor cells but also into tumor-supporting tissues and effector cells of the immune system. (Gómez-Navarro et al. 1999).

There are numerous factors that complicate therapeutic methods comprising gene delivery *in vivo* which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to, and the disease being treated.

Therefore, the specification as filed does not describe the full scope of the claimed invention, in a sufficient manner so as to enable one of ordinary skill in the art to practice the present invention without undue experimentation. These conclusions are based upon the known unpredictability regarding the delivery of therapeutic genes *in vivo,* the behavior of antisense oligonucleotides *in vivo* and further with providing a beneficial effect in a patient, and the lack of guidance in the specification as filed in this regard.

The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that a single endogenous gene is suppressed and replaced and the desired secondary effect (treatment leading to the amelioration of conditions associated with the expression of

said endogenous gene) is obtained. The specification as filed does not provide any guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 2-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Hartl et al. Claims 2-3 read on a medicament comprising either one or both of a gene suppressing agent and a nucleic acid encoding at least part of a gene product wherein the sequence differs from the endogenous gene in wobble sites. However, it is unclear if the replacement gene comprises a sequence that is different from the endogenous gene in all wobble sites. Claim 3 is interpreted as reading on nucleic acid wherein at least one wobble site is different from the endogenous gene.

Hart et al. disclose a gene therapy CFTR cDNA expression vector that comprises a sequence encoding CFTR wherein the sequence contains a silent point mutation at a wobble site (see Figure 1). This mutation did not alter the predicted amino acid sequence produced from the endogenous gene.

Hart et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L Epps whose telephone number is 703-308-8883. The examiner can normally be reached on Mondays through Friday, 9:00AM to 6:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

jle
February 7, 2001

ROBERT A. SCHWARTZMAN
PRIMARY EXAMINER

Notice to Comply	Application No. 09/155,708	Applicant(s) FARRAR et al.	
	Examiner J. Epps	Art Unit 1635	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other:

Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
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